MARKED-UP VERSION OF AMENDMENTS

Claim 9 has been canceled.

Claims 1, 4-6 and 10-11 have been amended as follows:

1. (Amended) An adenosine-5'-diphosphate (ADP)-ribosylation inhibitor comprising proanthocyanidin which has been purified to a tetramer or higher fraction as an effective ingredient.

4. (Twice Amended) An ADP-ribosylation inhibitor according to claim 1, wherein proanthocyanidin is the one extracted with at least one solvent selected from the group consisting of water, an alcohol, and ester and a ketone.

5. (Twice Amended) An ADP-ribosylation inhibitor according to claim 1, wherein proanthocyanidin is the one purified using a substance selected from the group consisting of a styrene ~~type~~ adsorption resin, an anionic exchange resin, an octadecyl-chemically binding ~~type~~ silica gel, an octyl-chemically binding ~~type~~ silica gel, a phenyl-chemically binding ~~type~~ silica gel and a silica gel.

6. (Twice Amended) A composition for the treatment and/or prevention of diphtheria, pertussis, tetanus and opportunistic infection, comprising as an effective ingredient an ADP-ribosylation inhibitor comprising proanthocyanidin which has been purified to a tetramer or higher fraction as an effective ingredient.

10. (Twice Amended) A composition for the treatment and/or prevention of enterotoxin type bacterial infectious disease according to claim 7, wherein proanthocyanidin is the one extracted with at least one solvent selected from the group consisting of water, an alcohol, an ester and a ketone.

11. (Twice Amended) A composition for the treatment and/or prevention of enterotoxin type bacterial infectious disease according to claim 7, wherein proanthocyanidin is the one purified using a substance selected from the group consisting of a styrene ~~type~~ adsorption resin, an anionic exchange resin, an octadecyl-chemically binding ~~type~~ silica gel, an octyl-chemically binding ~~type~~ silica gel, a phenyl-chemically binding ~~type~~ silica gel and a silica gel.

New claims 12-21 have been added as follows:

12. A composition for the treatment and/or prevention of enterotoxin type bacterial infectious disease according to claim 2, wherein proanthocyanidin is obtained from an edible plant or an edible plant-derived material.

13. A composition for the treatment and/or prevention of enterotoxin type bacterial infectious disease according to claim 12, wherein said edible plant or edible plant-derived material is an extract from an apple or a grape.

14. A composition for the treatment and/or prevention of enterotoxin type bacterial infectious disease according to claim 6, wherein the proanthocyanidin has been purified to a pentamer or higher fraction as an effective ingredient.

15. A composition for the treatment and/or prevention of enterotoxin type bacterial infectious disease according to claim 6, wherein the proanthocyanidin has been purified to hexamer and higher fractions as an effective ingredient.

16. An adenosine-5'-diphosphate (ADP)-riboslation inhibitor according to claim 1 comprising proanthocyanidin which has been purified to a pentamer or higher fraction as an effective ingredient.

17. An adenosine-5'-diphosphate (ADP)-riboslation inhibitor according to claim 1 comprising proanthocyanidin which has been purified to hexamer and higher fractions as an effective ingredient.

18. A method for the treatment and/or prevention of enterotoxin type bacterial infectious disease comprising proanthocyanidin as an effective ingredient, comprising administering to a patient in need of such treatment a composition comprising proanthocyanidin.

19. A method according to claim 18, wherein the bacterial infectious disease is cholera, botulinus or traveler's diarrhea.

20. A method according to claim 18, wherein proanthocyanidin has been purified to a pentamer or higher fraction.

21. A method according to claim 18, wherein proanthocyanidin has been purified to hexamer and higher fractions.

REMARKS

By the present amendment, claim 9 has been canceled, claims 1, 4-5 and 11 have been amended, and new claims 12-21 have been added. Support for the amendments is found in the original application. In particular, support for the added recitation in claim 1 and for claims 16-19 is provided in the original application, in particular on page 5, lines 16-20 and page 12, Table 1; support for claims 12-13 is found in original claims 2 and 9, respectively; support for claims 14-17 and 20-21 is found on page 5, lines 16-23 and page 12, Table 1; and support for claims 18-19 is found in original claims 7 and 8, respectively.

Claims 1-8 and 10-21 are pending in the present application. Claims 1-6 and 16-17 are directed to an adenosine-5'-diphosphate (ADP)-ribosylation inhibitor, claims 7-8 and 10-15 are directed to a composition for the treatment and/or prevention of bacteria infectious disease comprising such inhibitor, and claims 18-21 are directed to a method for the treatment and/or prevention of bacteria infectious disease using such a composition.

In the Office Action, claims 1-3 are rejected under 35 U.S.C. 102(b) as anticipated by U.S. Patent No. 5,912,363 (Nafisi-Movaghar). It is alleged in the Office Action that Nafisi-Movaghar discloses isolating proanthocyanidins from grape seeds.

Reconsideration and withdrawal of the rejection is respectfully requested. Nafisi-Movghar merely teaches the isolation of proanthocyanidin from seeds such as grape and its use as an anti-oxidizing agent without further purification of proanthocyanidin. Specifically, Nafisi-Movaghar discloses isolating proanthocyanidins from grape seeds by ultrafiltration, adsorption on an

adsorbent such as divinylbenzene, and elution with a polar solvent such as ethanol. This process is not particularly selective to higher polymer proanthocyanidin fractions, so that the isolation process of Nafisi-Movaghar fails to purify higher polymer proanthocyanidin fractions.

In contrast, the presently claimed composition comprises proanthocyanidin which as been purified to a tetramer or higher fraction, as recited in present claim 1. The test results shown on Table 1 clearly show that tetramer or higher proanthocyanidin fractions provide a considerably higher inhibition rate than lower polymer fractions. This feature of the presently claimed inhibitor and its advantages are not taught or suggested in Nafisi-Movaghar, which is not concerned about purifying a proanthocyanidin fraction or using proanthocyanidin against bacterial infectious diseases. Therefore, the present claims are not obvious over Nafisi-Movaghar.

In view of the above, it is submitted that the rejection should be withdrawn.

Next, in the Office Action, claims 6-8 are rejected under 35 U.S.C. 102(b) as anticipated by U.S. Patent No. 4,797,491 (Ariga). It is alleged in the Office Action that Ariga discloses a pharmaceutical composition comprising proanthocyanidins.

Reconsideration and withdrawal of the rejection is respectfully requested. Ariga discloses a composition comprising proanthocyanidin, which is used as antioxidant. Further, the only proanthocyanidin compositions which are actually disclosed in Ariga are limited to dimers, trimers and tetramers. Specifically, the proanthocyanidin compositions obtained in Ariga are dimeric in Preparation Example 1 (see col. 8, lines 35 and 39), dimeric and trimeric in Preparation Example 2 (see col. 8, line 65 and col. 9, line 1), tetrameric in Preparation Example 3 (see col. 9, line 19),

dimeric in Preparation Example 4 (see col. 9, line 49), dimeric and monomeric in Preparation Example 5 (see col. 10, line 25), and dimeric to tetrameric in Preparation Example 6 (see col. 10, line 48). Thus, Ariga does not disclose purified higher polymer proanthocyanidins. Accordingly, a person of ordinary skill in the art would not find any teaching in Ariga regarding a possible anti-oxidant activity of higher polymer proanthocyanidins. As a result, a person of ordinary skill in the art would not be motivated by Ariga to purify higher polymer factions, because that person would have no expectation of successfully obtaining an anti-oxidant composition.

In contrast, the present inventors have purified compositions containing proanthocyanidin which has been purified to tetramer or higher fractions, and found that such compositions are effective against bacterial infectious diseases. This feature of the present invention and its adavantages are not taught or suggested in Ariga, which focuses on lower polymer fractions and is silent as to higher polymer fractions. Therefore, the present claims are not anticipated by, and not obvious over, Ariga.

In view of the above, it is submitted that the rejection should be withdrawn.

Next, in the Office Action, claims 6-8 are rejected under 35 U.S.C. 112, first paragraph, as not enabled. It is alleged in the Office Action that the specification is enabling only for the treatment, not for the prevention, of enterotoxin type bacterial infectious disease.

The rejection is respectfully traversed. Both (i) the molecular cascade of the infection, and (ii) the blocking effect of the proanthocyanidins of the present invention, have been identified and explained in the specification. In view of this activity of the proanthocyanidins of the present

invention on the infection process, a person of ordinary skill in the art understands immediately that, since proanthocyanidins have a blocking effect for the treatment of an existing infection, they also have a blocking effect for the prevention of a later-occurring infection.

For example, reference is made to Test Example 2 in the present specification, which shows clearly that accumulation of fluid caused by the cholera toxin is substantially suppressed when the present poanthocyanidin is present with Vibrio cholera. This demonstrates that the cholera crisis was prevented when the rabbit was infected with Vibrio cholera. Thus, a person of ordinary skill in the art would understand that the proanthocyanidin of the present invention has a preventive as well as a treating effect.

In view of the above, it is submitted that the rejection should be withdrawn.

Next, in the Office Action, claims 4-5 and 9-11 are rejected under 35 U.S.C. 112, second paragraph, as indefinite. It is alleged in the Office Action that the terms "and ketone" in claim 4, "type" in claims 5 and 11 and "and a silica gel" in claim 11, "and a ketone" in claim 10, are unclear, and the phrase "said edible plant or edible plant-derived material" in claim 9 lacks antecedent basis.

Reconsideration and withdrawal of the rejection is respectfully requested. Present claims 4 and 10 recite "at least one solvent selected from the group consisting of water, an alcohol, an ester and a ketone," the term "type" has been deleted in claims 5 and 11, and present claim 11 recites "one purified using a substance selected from the group consisting of..." on line 3 to

introduce the following Markush group. Claim 9 has been canceled and new claims 12-13 have been added, which correspond to claims 2-3 but depend directly or indirectly on claim 7.

In view of the above, it is submitted that the rejection should be withdrawn.

Finally, regarding method claims 18-21, it is submitted that a function of proanthocyanidins as an ADP-ribosylation inhibitor is without connection with a function as anti-oxidizing agent. Specifically, the inactivation of ADP-ribosylation activity occurs by bonding between the proanthocyanidin and a bacterial toxin such subunit A of cholera toxin, in which process anti-oxidizing properties are not involved. Two articles by Su-Chen Tsai et al. and Yanagida et al., respectively, are submitted for general information on this point. Thus, it is submitted that claims 18-21 are patentable over the cited references.

In conclusion, the invention as presently claimed is patentable. It is believed that the claims are in allowable condition and a notice to that effect is earnestly requested.

In the event there is, in the Examiner's opinion, any outstanding issue and such issue may be resolved by means of a telephone interview, the Examiner is respectfully requested to contact the undersigned attorney at the telephone number listed below.

In the event this paper is not considered to be timely filed, the Applicants hereby petition for an appropriate extension of the response period. Please charge the fee for such extension and any other fees which may be required to our Deposit Account No. 01-2340.

Respectfully submitted,

ARMSTRONG, WESTERMAN & HATTORI, LLP

By: _____

Nicolas E. Seckel
Attorney for Applicants
Reg. No. 44,373

Atty. Docket No. 010969

Suite 1000
1725 K Street, N.W.
Washington, D.C. 20006
Tel: (202) 659-2930
Fax: (202) 887-0357

NES:rep

Encls.: Su-Chen Tsai et al. Article
Yanagida et al. Article

H:\HOME\NES\DOC\2000\010969-AMD first OA.wpd